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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
AEDER, SEAN E	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 04/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/930,559	DAWSON ET AL.	
	Examiner	Art Unit	
	Sean E. Aeder, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-57* is/are pending in the application.

4a) Of the above claim(s) *7,13,14,26,28-31,40,41 and 47-57* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8-12,15-25,27,32-39 and 42-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 August 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

The Election filed 12/27/05 in response to the Office Action of 5/17/05 is acknowledged and has been entered. Applicant elected group III with traverse.

The traversal is on the ground(s) that group I necessarily includes group III. Thus, searching the two groups together would not be a serious burden. This argument is found persuasive and a final restriction is made after rejoining groups I and III. Therefore, the combined group is specifically drawn to a method of inhibiting cancer cells comprising administering a composition comprising a PPT1 modulator comprising a peptide that comprises at least or at most 5 contiguous amino acids from SEQ ID NO:3 and a method of inhibiting cancer cells comprising administering a composition comprising a PPT1 modulator comprising DAP1.

Claims 1-57 are pending.

Claims 7, 13, 14, 26, 28-31, 40, 41, and 47-57 are withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to a non-elected invention.

Claims 1-6, 8-12, 15-25, 27, 32-39, and 42-46 are currently under consideration.

Specification

The specification is objected to because it contains embedded hyperlinks and/or other form of browser-executable codes (page 76 line 28; page 155 line 7). Applicant is required to delete all embedded hyperlinks and/or other form of browser-executable codes. See MPEP § 608.01.

The specification is objected to on pages 6, 7, 8, 11, 13, 17, 28, 43, 135, 136, 139, 140, 141, 149, 152, and 158 for improper disclosure of polypeptide sequences, as it fails to comply with the requirements of 37 CFR 1.821 through 1.825. This definition sets forth limits, in terms of numbers of amino acids and/or numbers of nucleotides, at or above which compliance with the sequence rules is required. Nucleotide and/or amino acid sequences as used in 37 CFR 1.821 through 1.825 are interpreted to mean an unbranched sequence of four or more amino acids or an unbranched sequence of ten or more nucleotides. (see MPEP 2422). Proper correction is required.

Drawings

The drawings submitted on 8/15/01 are objected to because Figure 3B and Figure 14 improperly disclose polypeptide sequences, as they fail to comply with the requirements of 37 CFR 1.825 through 1.825. (see MPEP 2422). Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement

sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claims

Claim 39 is objected to for improper disclosure of polypeptide sequences, as it fails to comply with the requirements of 37 CFR 1.821 through 1.825. (see MPEP 2422). Proper correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 22, 23, 44, and 45 are rejected as vague and indefinite for reciting the term DAP1 as the sole means of identifying the claimed PPT1 modulator. The use of laboratory designations only to identify a particular molecule renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct molecules. For example, Feinstein et al (Genomics, 1995, 29:305-307) teach DAP1 is a naturally-occurring protein (see page 305, in particular), while the instant specification and other teachings by Cho et al (Journal of

Neuroscience, 2000, 62:234-240) teach DAP1 is the lipopeptide synthetic inhibitor AcG-palmitoyl diaminoproprionate-VKIKK (abstract of Cho et al; and page 7 lines 9-12, in particular). Amending the claims to specifically and uniquely identify DAP1 as the synthetic inhibitor AcG-palmitoyl diaminoproprionate-VKIKK can obviate the rejection.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6, 8-11, 15-21, 24, 27, 32-38, 42, 43, and 46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In the instant case, the claims are inclusive of a genus of "PPT1 modulators". However, the written description in this case only sets forth the PPT1 modulator DAP1, peptide mimetics of the amino acid sequence VKIKK (SEQ ID NO:12), and Didemnin B. The specification does not disclose any other PPT1 modulators, including other peptides or peptide mimetics of any other sequences, as broadly encompassed in the claims.

The specification teaches PPT1 modulators include any molecule that selectively, competitively, or specifically interacts with PPT1 and specifically inhibits or enhances its activity. Further, the specification discloses that PPT1 modulators may be a protein or a peptide, a small molecule, or a nucleic acid molecule (page 6 lines 14-18,

in particular). However, the written description only reasonably conveys the PPT1 modulator DAP1 (pages 152-153 and pages 158-159, in particular) peptide mimetics of the amino acid sequence VKIKK (SEQ ID NO:12) (claim 25, in particular), and Didemnin B (page 4, in particular). A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or by describing structural features common to that genus that "constitute a substantial portion of the genus." See University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997): "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNA, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus."

The court has since clarified that this standard applies to compounds other than cDNAs. See University of Rochester v. G.D. Searle & Co., Inc., F.3d, 2004 WL 260813, at *9 (Fed.Cir.Feb. 13, 2004). The instant specification fails to provide sufficient descriptive information, such as definitive structural features that are common to the genus. That is, the specification provides neither a representative number of species that encompass the genus of PPT1 modulators nor does it provide a description of structural features that are common to PPT1 modulators. Further, the specification does not provide a written description of any other specific peptide mimetic that modulates PPT1 other than a peptide mimetic of VKIKK (SEQ ID NO:12). Since the disclosure fails to describe common attributes or characteristics that identify members

of the genus, and because the genus is highly variant, the disclosure of DAP1, peptide mimetics of the amino acid sequence VKIKK (SEQ ID NO:12), and Didemnin B is insufficient to describe the genus. Thus, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of PPT1 modulators, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolation. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only PPT1 modulators wherein said PPT1 modulators are DAP1, peptide mimetics of the amino acid sequence VKIKK (SEQ ID NO:12), or Didemnin B, but not the full breadth of the claims, meet the written description provision of 35 U.S.C. 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 1-6, 8-12, 15-25, 27, 32-39, and 42-46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention as broadly claimed.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the

invention based on the content of the disclosure. See also *Ex parte* Forman, 230 USPQ 546 (BPAI 1986).

The claims are broadly drawn to a method of inhibiting *any* activity of *any* type of cancer cell in vitro *and in an animal* comprising administering to the cancer cell *any* PPT1 modulator.

The specification discloses a method of *inhibiting cell survival and inhibiting cell proliferation* in several cancer cell lines grown *in vitro* comprising administering to said cells the PPT1 modulator DAP1 (pages 152-154 and pages 157-159, in particular). Further, the prior art discloses a method of inhibiting cell proliferation in a leukemia cell line grown in vitro comprising administering the PPT1 modulator Didemnin B (see Rinehart et al (Science, 1981, 22(4497): 933-935) as evidenced by Meng et al (Biochemisty, 1998, (37): 10488-10492)). However, the specification does not provide any working examples demonstrating that DAP1 inhibits any activity other than cell survival and cell proliferation. Further, the specification does not provide any working examples demonstrating that Didemnin B inhibits any activity other than cell proliferation. Further, the specification provides prophetic guidance for administering DAP1 to an animal (Example 4); however, the specification does not provide any working examples that would indicate DAP1 or Didemnin B would predictably inhibit *any* activity of a cancer cell *in an animal*. Further, the specification provides no indication that any PPT1 modulator of the elected group other than DAP1 or Didemnin B that would predictably inhibit an activity of a cancer cell grown in vitro or found in an animal.

Although Applicant is enabled for a method of inhibiting certain properties of cancer cells grown in vitro by treating said cells with DAP1 or Didemnin B, Applicant is not enabled for a method of inhibiting any activity of any type of cancer cell found in an animal comprising administering any PPT1 modulator of the elected group. Those of skill in the art recognize that in vitro assays and cell culture based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the in vivo environment as compared to the very narrowly defined and controlled conditions of an in-vitro assay does not permit a single extrapolation of an in vitro assay to human diagnostic efficacy with any reasonable degree of predictability. In vitro assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore, it is well know in the art that cultured cells, over a period of time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts in vivo. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation in vivo. Without this control, cellular metabolism may be more constant in vitro but may not be truly representative of the tissue from which the cells were derived. This has

often led to tissue culture being regarded in a rather skeptical light (p.4, see Major Difference In Vitro). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, "Petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells in vivo are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well know in the art that cells in culture exhibit characteristics different from those in vivo and cannot duplicate the complex conditions of the in vivo environment involved in host-tumor and cell-cell interactions.

Further, treatment of cancer in general is at most unpredictable, as underscored by Gura (Science, 1997, 278:1041-1042.) who discusses the potential shortcoming of potential anti-cancer agents including extrapolating from in-vitro to in-vivo protocols, the problems of drug testing in knockout mice, and problems associated with cologenic assays. Indeed, since formal screening began in 1955, thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the FDA (page 1041 first column, in particular) wherein the fundamental problem in drug discovery for cancer is that the model systems are **not predictive**. All of this underscores the

criticality of providing workable examples which is not disclosed in the specification, particularly in an unpredictable art, such as cancer therapy.

In view of the teachings above and the lack of guidance, workable examples and/or exemplification in the specification, it would require undue experimentation by one of skill in the art to determine with any predictability, that the method would function as claimed. Thus, while the specification is enabling for a method of *inhibiting cell survival* and *inhibiting cell proliferation* of *cultured cancer cell lines grown in vitro* by administering *DAP1 or Didemnin B*, the specification lacks reasonable guidance, predictability, and objective evidence that enables a method of inhibiting any activity other than cell survival and cell proliferation of cancer cells cultured in vitro. Further, the specification lacks reasonable guidance, predictability, and objective evidence that the method would function as claimed in an animal or that the method would function as claimed in vitro using any PPT1 modulator of the elected invention other than DAP1 or Didemnin B.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 3, 5, 8, 9 rejected under 35 U.S.C. 102(b) as being anticipated by Rinehart et al (Science, 1981, 22(4497): 933-935) as evidenced by Meng et al (Biochemisty, 1998, (37): 10488-10492).

The claims are drawn to a method of inhibiting the proliferation of a cancer cell comprising administering to said cell a composition comprising a proteinaceuous PPT1 modulator that selectively interacts with and inhibits the activity of PPT1.

Rinehart et al teaches a method of inhibiting leukemia cell proliferation comprising administering Didemnin B (see page 212 last paragraph, in particular). Further, Rinehart et al teaches Didemnin B is a proteinaceuous compound (see Figure 1, in particular). Further, as evidenced by Meng et al, Didemnin B functions as an agonist that selectively interacts with and inhibits the activity of PPT1 (see abstract of Meng et al, in particular).

Summary

No claim is allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean E. Aeder, Ph.D. whose telephone number is 571-272-8787. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SEA

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SUPERVISORY PATENT EXAMINER